Prion protein preamyloid and amyloid deposits in Gerstmann-Sträussler-Scheinker disease, Indiana kindred.

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Abstract

Gerstmann-Sträussler-Scheinker disease (GSS) is a familial neurological disorder pathologically characterized by amyloid deposition in the cerebrum and cerebellum. In GSS, the amyloid is immunoreactive to antisera raised against the prion protein (PrP) 27-30, a proteinase K-resistant peptide of 27-30 kDa that is derived by limited proteolysis from an abnormal isoform of a neuronal sialoglycoprotein of 33-35 kDa designated PrPSc. Polyclonal antibodies raised against synthetic peptides homologous to residues 15-40 (P2), 90-102 (P1), and 220-232 (P3) of the amino acid sequence deduced from hamster PrP cDNA were used to investigate immunohistochemically the distribution of PrP and PrP fragments in the brains of two patients from the Indiana kindred of GSS. Two types of anti-PrP-immunoreactive deposits were found: (i) amyloid deposits, which were exclusively labeled by anti-P1 antiserum to residues 90-102 of PrP, and (ii) preamyloid deposits, which were labeled by all anti-PrP antisera but did not exhibit the tinctorial and optical properties of amyloid. The latter appeared as diffuse immunostaining of the neuropil that targeted to areas in which amyloid deposits were most abundant. They were partially resistant to proteinase K digestion and consisted ultrastructurally of amorphous, flaky, electron-dense material. These findings substantiate our previous observation that the major amyloid component in the GSS Indiana kindred is an internal fragment of PrP and indicate that full-length abnormal isoforms of PrP and/or large PrP fragments accumulate in brain regions most affected by amyloid deposition. These findings support the view that in the GSS Indiana kindred a stepwise degradation of PrP occurs in situ in the process of amyloid fibril formation.

MeSH

Aged; Amyloid; Cerebellum; Gerstmann-Straussler-Scheinker Disease; Human; Indiana; Microscopy, Electron; PrPSc Proteins; Prions; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.

depicted as cylinders. The inner cytoplasmically oriented NBFs are shown as hatched spheres with slots to indicate the means of entry by the nucleotide. The large polar R-domain which links the two halves is represented by an stippled sphere. Charged individual amino acids within the transmembrane segments and on the R-domain surface are depicted as small circles containing the charge sign. Net charges on the internal and external loops joining the membrane cylinders and on regions of the NBFs are contained in open squares. Sites for phosphorylation by protein kinases A or C are shown by closed and open triangles respectively. K,R,H,D, and E are standard nomenclature for the amino acids, lysine, arginine, histidine, aspartic acid and glutamic acid respectively.

Each of the predicted membrane-associated regions of the CFTR protein consists of 6 highly hydrophobic segments capable of spanning a lipid bilayer according to the algorithms of Kyte and Doolittle and of Garnier et al (J. Mol. Biol. 120, 97 (1978) (Figure 13). The membrane-associated regions are each followed by a large hydrophilic region containing the NBFs. Based on sequence alignment with other known nucleotide binding proteins, each of the putative NBFs in CFTR comprises at least 150 residues (Figure 13). The 3 bp deletion at position 507 as detected in CF patients is located between the 2 most highly conserved segments of the first NBF in CFTR. The amino acid sequence identity between the region surrounding the isoleucine deletion and the corresponding regions of a number of other proteins suggests that this region is of functional importance (Figure 15). A hydrophobic amino acid, usually one with an aromatic side chain, is present in most of these proteins at the position corresponding to I507 of the CFTR protein. It is understood that amino acid polymorphisms may exist as a result of DNA polymorphisms. Similarly, mutations at the other positions in the